REMARKS

Claims 49, 100, 110, 111, 118, 119 and 123 have been amended in the instant amendment. Claims 65-68 have been canceled. Claims 49, 53-55, 59-64, 100, 102-107, 110-112, 114-119 and 123 are pending and under consideration.

I. AMENDMENT TO THE CLAIMS

Claims 65-68 have been canceled without prejudice to Applicants' right to pursue canceled subject matter in one or more related applications.

Claims 49, 110, 111, 118 and 119 have been amended without prejudice to Applicants' right to pursue deleted subject matter in one or more related applications.

Support for the amendments to claims 100 and 123 are found in the specification, for example, at page 6, lines 11-26, and page 16, lines 10-15.

As the above amendments to claims are fully supported by the specification and claims as originally filed, entry thereof is respectfully requested. No new matter has been added. No amendment fee is believed to be due.

II. PRIORITY

Applicants respectfully maintain that the instant application is a continuation-in-part of U.S. Application No. 08/724,394 filed October 1, 1996, now U.S. Patent No. 5,872,237 issued February 16, 1999, which is a continuation-in-part of U.S. Application No. 08/630,912, now abandoned, and U.S. Application No. 08/652,265, now U.S. Patent No. 6,025,130 issued February 15, 2000.

III. REJECTION OF CLAIMS 65-68 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 65-68 stand rejected under 35 U.S.C. § 112, first paragraph, allegedly for lack of written description. (The Patent Office refers to this rejection as a "new matter" rejection). Applicants respectfully disagree and do not acquiesce in this rejection. Nonetheless, in order to expedite prosecution, Applicants have canceled claims 65-68 and submit that the rejection to these claims is moot in view of their cancellation. Applicants respectfully request the withdrawal of the rejection of claims 65-68 under 35U.S.C. § 112, first paragraph.

IV. REJECTION OF CLAIMS 100, 102-107, 110-112, 114-119, AND 123 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 100, 102-107, 110-112, 114-119 and 123 stand rejected under 35 U.S.C. § 112, first paragraph, allegedly for lack of written description. (Applicants assume that the Patent Office made a typographical error and meant to include claim 100 in the rejection rather than twice indicate claim 110). Applicants respectfully traverse the rejection.

The Patent Office alleges that Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus. The Patent Office refers to the Written Description guidelines. Indeed, the Federal Circuit adopted the Patent Office's guidelines that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics." *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002) (quoting Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, 1 "Written Description" Requirement, 66 Fed.Reg. 1009, 1106 (Jan. 5, 2001)). In *Enzo Biochem*, the Federal Circuit found that the written description requirement would be met for all of the claims drawn to oligonucleotides if the functional characteristic of preferential binding to *N. gonorrhoeae* over the *N. meningitidis* were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed. *Id.* at 1613.

Turning to instant amended claims 100 and 123 (and claims depending therefrom), Applicants respectfully submit that the written description requirement is met since the functional characteristic of selective hybridization to the target sequence in SEQ ID NO: 2 over SEQ ID NO: 1 is coupled with the disclosures of the sequences of SEQ ID NO:2 and SEQ ID NO:1 in the specification. Outside of the polymorphic sites, SEQ ID NO: 1 and SEQ ID NO:2 are identical. Applicants respectfully submit that, the skilled artisan would not expect substantial variation among species of oligonucleotides directed towards any one SNP as encompassed in the claims because of the selective hybridization requirement. This is because the recited oligonucleotides have to be structurally similar in order to bind the particular allele in the SEQ ID NO:2 sequence or its complement under conditions in which the oligonucleotides do not hybridize to SEQ ID NO:1 or its complement.

Applicants respectfully submit that a representative number of species are disclosed, since stringent hybridization conditions in combination with the selective hybridization to

SEQ ID NO:2 over SEQ ID NO:1 and level of skill and knowledge in the art are adequate to determine that Applicants were in possession of the claimed inventions. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 100, 102-107, 110-112, 114-119, and 123 under 35 U.S.C. § 112, first paragraph.

V. REJECTION OF CLAIMS 49, 53-55, 59-68, 100, 102-107, 110-112, 114-119 AND 123 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 49, 53-55, 59-68, 100, 102-107, 110-112, 114-119 and 123 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Applicants respectfully traverse the rejection.

Enablement under 35 U.S.C. § 112, first paragraph, requires that the specification teach those in the art to make and use the invention without undue experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The Federal Circuit elaborated that whether undue experimentation is needed is not a single, simple factual determination, but a conclusion reached by weighing many factual considerations, and listed eight exemplary factors (the "*Wands* factors"). *Id.* The Patent Office purports to apply the *Wands* factors to arrive at its allegation that undue experimentation is required to practice the instant claims. Applicants respectfully submit that an analysis of the *Wands* factors requires the opposite conclusion.

From the outset, Applicants note that the decision of *In Wands* applies to the question of whether undue experimentation is required to *practice* the invention. The comments in the Office Action, however, seem to be geared towards whether the claimed invention would be found useful. For example, the Patent Office alleges that the "skilled artisan would be required to perform additional undue experimentation to determine whether SNPs [at the recited positions] would be useful for any particular means." *See* Office Action, page 10. The standard for usefulness in connection with the enablement requirement was directly addressed in *In re Brana* in which the Federal Circuit stated:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

See In re Brana, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995). The instant specification teaches novel polymorphic sites that "provide surrogate markers for use in diagnostic assay to

detect the likely presence of the mutation 24d1 and/or 24d2, preferably 24d1, in homozygotes or heterozygotes." *See* page 11, lines 32-35. HH gene mutation 24d1 is gives rise to the majority of disease-causing chromosomes present in the population today and the mutation results in a Cys282Tyr substitution in the mutant HH gene product. *See* specification, page 2, lines 13-17, and page 28, line 4. Table 1 of the specification lists the novel polymorphic sites. Table 2 of the specification lists the frequencies of selected alleles defined by the polymorphic sites of the invention in the general population. *See* page 12, lines 21-23. Preferred alleles have a frequency of 25% or less (see page 12, lines 29-31) and each of the polymorphic sites recited in the instant claims have a frequency of 25% or less. The specification continues that "[i]t will be understood by those of skill in the art that because [the polymorphic sites] were identified in an ancestral HH homozygote, the haplotypes defined by the polymorphic sites of Table 1 are predictive of the likely presence of the HH gene mutation 24d1." *See* page 12, lines 34-38. Furthermore, the likelihood of a carrier of the ancestral gene mutation carrying a combination of two, three or more of <u>any</u> polymorphic alleles is greater than that of a person who is not a carrier. *See* page 12, lines 1-6. Thus, the specification teaches the usefulness of the instant polymorphic sites as surrogate markers. The Patent Office has not presented any reason to doubt the objective truth of the statements contained in the specification.

The Patent Office states that the specification fails to provide an association of the SNPs at the recited positions with any particular disease or condition. *See* Office Action, page 9. The pertinence of this comment is lost on Applicants since the claims do not recite such a requirement, nor to Applicants' knowledge is such a requirement imposed in law or in fact that a surrogate marker itself has to be a direct cause of any particular disease or condition. Again, the specification teaches that the surrogate markers recited in the claims are predictive of the likely presence of the HH gene mutation 24d1. Thus, Applicants respectfully submit, those of ordinary skill in the art would recognize the use of the subject matter of the instant claims.

For the reasons discussed above, Applicants respectfully submit that those of skill in the art would know how to use the inventions of claims 49, 53-55, 59-68, 100, 102-107, 110-112, 114-119 and 123. Hence, the non-enablement rejection is legally improper and should be withdrawn.

The Patent Office also acknowledges that the specification is enabling for isolated polynucleotides of 10 nucleotides in length and isolated polynucleotides of at least 18 consecutive bases which span SNPs 35983 and 61465. As indicated in Table 2, the

HH-associated allelic variants of these SNPs are relatively rare in random chromosomes. The specification teaches that HH-associated allelic variants of SNPs 35983 and 61465 occur in a majority of HH patients. *See* page 28, line 30, to page 30, line 9. Thus, these results with regard to SNPs 35983 and 61465 are indicative that allelic variants of SNPs in the HH-affected chromosome that are relatively rare in chromosomes from a random population are likely to present in much greater frequencies in HH-affected chromosomes. As explained in the specification, the HH-associated alleles at SNPs 230376, 214795, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 40431, and 38526 are relatively rare in random chromosomes. *See* page 12, lines 21-31, and Table 2. The Patent Office provides no reason to dispute the data provided in the specification. On this basis alone, the rejection of claims 49, 53-55, 59-68, 100, 102-107, 110-112, 114-119 and 123 for lack of enablement should be withdrawn. Nonetheless, below Applicants respond to the remarks presented by the Patent Office in connection to the *Wands* factors.

i. Breadth of the claims--The Patent Office indicated that the recited SNPs are "within SEQ ID NO: 1." SEQ ID NO: 1 (*i.e.*, Figure 1) is a sequence from an unaffected individual, whereas SEQ ID NO:2 (*i.e.*, Figure 2) is a sequence from an HH affected individual homozygous for the ancestral HH mutation and region. *See* specification, page 4, line 36-38 and page 24, line 33, to page 25, line 5.. Thus, while the SNPs are numbered according to their corresponding position in SEQ ID NO:1, the particular alleles in the SNPs indicative of the presence of the disease-causing HH gene mutation 24d1 are located "within" SEQ ID NO:2. Nonetheless, since the entire sequences of both SEQ ID NO:1 and SEQ ID NO:2 are provided, Applicants respectfully submit that the claims are fully enabled for those of skill in the art to make and use the isolated polypeptides, kits and arrays of the instant claims without undue experimentation.

ii. Nature of the Invention--The Patent Office generalizes that the instant claims are in a class of invention characterized as unpredictable. Yet the Patent Office does not suggest that preparing the isolated polynucleotides, kits and arrays as recited in the claims would entail any undue experimentation on the part of a person of skill in the art. Applicants respectfully submit that a consideration of the Nature of the Invention *Wands* factor does not fairly undue experimentation is necessary to the practice of the claims.

iii. Predictability or Unpredictability of the Art and State of the Art--The instant claims encompass oligonucleotides or isolated polynucleotides useful for detecting surrogate markers predictive of whether a subject is a carrier of the ancestral 24d1 mutation. To be clear, it is Applicants' understanding that the Patent Office does not dispute the association of

the 24d1 mutation and hereditary hemochromatosis susceptibility. Nor does the Patent Office appear to doubt that the recited polypeptides, kits and arrays would be able to used to detect the recited SNPs without undue experimentation. Instead, the Patent Office refers to various publications that caution drawing conclusions between a genetic variant and disease susceptibility in general. However, the specific usefulness of the instant surrogate markers is that they have predictive value for the presence of the ancestral 24d1 mutation, as explained above. There is no requirement that one of skill in the art needs to predict the genetic effects of the recited SNPs themselves on disease susceptibility in order to practice the instant claims.

Applicants respectfully submit that the *Wands* factors of the Predictability or Unpredictability of the Art and the State of the Art weigh in Applicants' favor that practice of the instant claims require no undue experimentation.

iv. Guidance in the Specification, Presence or Absence of Working Examples, Quantity of Experimentation, and Level of Skill in the Art--The Patent Office alleges that the claims "require the skilled artisan to determine whether the polymorphisms are associated with additional diseases without a reasonable expectation of success." Again, this is not a requirement to practice the instant claims. The specification identifies new polymorphisms found in the region of the HH gene that are present in the DNA of an individual known to carry the ancestral 24d1 mutation and be afflicted with hereditary hemochromatosis. *See* page 11, line 25, to page 12, line 4. Since the polymorphisms were identified in an HH ancestral HH homozygote, the haplotypes defined by the polymorphic sites of Table 1 are predictive of the likely presence of the HH gene mutation 24d1. *See* page 12, lines 34-38. Thus, the likelihood of a carrier of the ancestral gene mutation carrying a combination of two, three or more of <u>any</u> polymorphic alleles is greater than that of a person who is not a carrier. *See* page 12, lines 1-6. Moreover, an arbitrary group of the polymorphisms were characterized for their frequencies in the general population. *See* page 27, lines 30-35 and Table 2. Those polymorphisms that are less common in the general population are preferred. *See* page 12, lines 21-33. Certain polymorphic alleles identified as being less common in the general population are recited in the instant claims. As evidence that, in fact, a polymorphism identified as being less common in the general population is therefore enriched in hemochromatosis patients as compared to the general population, the frequencies of two polymorphisms occurring at bases 35983 and 61465 were compared in hemochromatosis patients to random individuals. The results indicated that the 35983 and 61465 SNPs are in fact, more common in hemochromatosis patients. *See* page 27, line 30, to

page 29, line 12. The Patent Office presents no reason to think that any of the other recited SNPs would not likewise be enriched in hemochromatosis patients, nor why such SNPs would not be a likely indicator of the presence of the ancestral HH mutation.

That the Patent Office appears to have missed the predictive value of the recited SNPs is suggested by the first full paragraph on page 11 of the Office Action. Here, the Patent Office alleges that it is unclear how the skilled artisan would use an oligonucleotide containing an "A" or "G" SNP occurring at base position 35983 of SEQ ID NO:1. The Patent Office suggests that only alleles "T" and "C" have use since only these have been shown to exist in nature. Furthermore, the Patent Office states that "it is unclear how the skilled artisan would use a sequence which does not appear to occur in the random chromosome population." In response, Applicants note that possible bases present in SNP 35983 include "A" which occurs in SEQ ID NO:1 and "T" which is in the complement to SEQ ID NO:1, as well as "G" that is present in SEQ ID NO:2 and "C" is present in the complement to SEQ ID NO: 2. As chromosomal DNA is double-stranded and both SEQ ID NOS: 1 and 2 are obtained from individuals, therefore each of the four bases do exist at SNP 35983 in nature. The specification teaches that the "G" SNP (or "C" SNP depending upon which strand is being considered) is not common in the general population, but is known to be present with the ancestral HH gene mutation. *See* page 27, line 38 to page 28, line 1, and Tables 1 and 2. Therefore, detecting the presence of the "G" SNP at position 35983 (or "C" in the opposite strand) in a subject's DNA provides an indicator that the subject may be more likely to be a carrier of the ancestral HH mutation than somebody with the "A" allele at that same position (or "T", depending upon which strand is being targeted for analysis). Applicants respectfully submit that the skilled artisan would know how make and use the claimed oligonucleotides.

Applicants respectfully submit the *Wands* factors of the Guidance in the Specification, Presence or Absence of Working Examples, Quantity of Experimentation, and Level of Skill in the Art do not support a finding of undue experimentation for the instant claims.

Applicants respectfully submit that the *Wands* factors weigh against a finding of undue experimentation for the instant claims. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 49, 53-55, 59-68, 100, 102-107, 110-112, 114-119 and 123 under 35 U.S.C. § 112, first paragraph.

VI. CLAIM REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

A. Claims 100, 102-107, and 110-111

Claims 100, 102-107, and 110-111 stand rejected under 35 U.S.C. § 112, second paragraph, allegedly as being indefinite. In particular, the Patent Office alleges that it is unclear whether the oligonucleotide hybridizes at a single site or over a target which comprises a SNP site, and whether the oligonucleotides must contain a "mutant" allele or "normal" allele. Applicants respectfully submit that the rejection is obviated by the instant amendment to claim 100. Applicants respectfully request that the rejection of claims 100, 102-107, and 110-111 under 35 U.S.C. § 112, second paragraph, be withdrawn.

B. Claims 123, 112, and 114-119

Claims 123, 112, and 114-119 stand rejected under 35 U.S.C. § 112, second paragraph, allegedly as being indefinite. In particular, the Patent Office alleges that it is unclear whether the oligonucleotide hybridizes to a particular allele at a SNP site in SEQ ID NO:1. Applicants respectfully submit that the rejection is obviated by the instant amendment to claim 123. Applicants respectfully request that the rejection of claims 123, 112, and 114-119 under 35 U.S.C. § 112, second paragraph, be withdrawn.

VII. CLAIM REJECTION UNDER 35 U.S.C. § 102

Claim 49 stands rejected under 35 U.S.C. § 102(b) allegedly as being anticipated by Brennan (U.S. Patent No. 5,474,796) or else as being anticipated by Pease *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:5022-5026. The rejection should be withdrawn, as discussed below.

A. Brennan (U.S. Patent No. 5,474,796)

Claim 49 stands rejected under 35 U.S.C. § 102(b) allegedly as anticipated by Brennan (U.S. Patent No. 5,474,796). The Patent Office alleges that Brennan teaches every possible 10-mer nucleic acid. Applicants respectfully traverse since Brennan does not teach or suggest every limitation of amended claim 49.

Applicants respectfully submit that the Patent Office is in error by indicating that Brennan actually constructed an array containing every possible permutation of 10-mer oligonucleotides (which would be 4^{10} oligonucleotides). In fact, Brennan merely describes in prophetic Example 4 every possible trimer (all 4^3 or 64 possible trimer oligonucleotides are shown in Figure 1b of Brennan). While Brennan does state that "[t]he array contains oligonucleotides having 10 nucleotides each (10-mer)" (col. 9, line 48) nowhere does

Brennan teach or suggest such an array with every possible 10-mer. This is clear from reading Example 4 of Brennan in its entirety.

In particular, using prophetic language, Brennan describes the use of oligonucleotide array plates to determine the nucleotide sequence of a target nucleic acid having 10 nucleotides. Col. 9, beginning at line 15 (under the heading "EXAMPLE 4"). Brennan states that the "synthesis is carried out such that each oligonucleotide element, moving in a 5'-3' direction, is identical to the preceding element in nucleotide sequence, except that it deletes the 5'-most nucleotide, and adds a new 3'-most oligonucleotide." Col. 9, lines 49-53. By reference to column 10, line 3 and to Figure 1, particularly Figure 1C, it is clear that an "element" is a trimer. Since any 10-mer oligonucleotide contains a series of trimers and the array contains every possible trimer, therefore, as Brennan states "[i]n this way the total array represents every possible permutation of *the* 10-mer oligonucleotide" Col. 9, lines 53-55 (emphasis added). The 10-mer oligonucleotide is ATTCTTGTTA, and obviously not every possible 10-mer is made "since the pattern of binding [to the array] is assessed and nucleotide sequence of the probe nucleic acid is determined by ordering the nucleotide sequence according to the known sequences of the oligonucleotide elements as shown in Figure 1." Col. 9, line 67, to Col. 10, line 5. Clearly, if every 10-mer had been placed on an array there would be no need to determine the sequence by ordering the known sequence of oligonucleotide elements. Nowhere does Brennan teach or suggest every possible 10-mer nucleic acid. Nor does it appear that Brennan actually synthesized an oligonucleotide given the prophetic language. Therefore the only 10-mer taught or suggested by Brennan is ATTCTTGTTA.

Amended claim 49 recites an isolated polynucleotide consisting of at least 8 consecutive bases to about 100 consecutive bases of SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one single nucleotide polymorphism (SNP) selected from a group consisting of SNPs at positions 230376, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 and 35983 of SEQ ID NO: 1, wherein said SNPs are found in a general human population with about 25% or less frequency. Applicants calculate that 480 decanucleotides are encompassed in amended claim 49, calculated as follows: 10 decanucleotides per sequence including a single SNP x 2 allelic forms x 2 for the complements thereof x 12 different SNPs. Upon inspection of sequences near the twelve SNP sites in SEQ ID NO:1, Applicants respectfully submit that the sequence ATTCTTGTTA is not included among the possible 480 decanucleotides. The Patent Office has not indicated otherwise.

Applicants respectfully submit that Brennan does not anticipate the isolated polynucleotide recited in amended claim 49. Accordingly, Applicants respectfully request that the rejection of claim 49 under 35 U.S.C. § 102(b) be withdrawn.

B. Pease *et al.*

Claim 49 stands rejected under 35 U.S.C. § 102(b) allegedly as anticipated by Pease *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:5022-5026. The Patent Office alleges that Pease *et al.* teach an oligonucleotide array of with every possible 8-mer. This is factually incorrect. Applicants respectfully traverse the rejection.

Pease *et al.* teach an array of all 4^4 (256) possible tetranucleotides (*i.e.*, 4-mers) "flanked by CG at the 3' and 5' ends." *See* page 5025, col. 1, last paragraph, and fig. 5. In other words, Pease *et al.* synthesized all oligonucleotides of the formula 5'-GCXXXXGC-3' where X may be A, C, T, or G. Thus, the array merely contains 256 octanucleotides (*i.e.*, 8-mers), which is clearly not the total number of all possible 4^8 or 65,536 octanucleotides. Pease *et al.* discuss the mere possibilities of manufacturing arrays having all possible 4^8 octanucleotides or 4^{12} dodecanucleotides. *See* page 5025, col. 2, first full paragraph.

Amended claim 49 recites an isolated polynucleotide consisting of at least 8 consecutive bases to about 100 consecutive bases of SEQ ID NOS:1 or 2, or the complement thereof, wherein said isolated polynucleotide includes at least one single nucleotide polymorphism (SNP) selected from a group consisting of SNPs at positions 230376, 207400, 200027, 195404, 160007, 125581, 120853, 96315, 61465, 40431, 38526 and 35983 of SEQ ID NO: 1, wherein said SNPs are found in a general human population with about 25% or less frequency. Applicants calculate that 384 octanucleotides are encompassed in amended claim 49, calculated as follows: 8 octanucleotides per sequence including a single SNP x 2 allelic forms x 2 for the complements thereof x 12 different SNPs. Upon inspection of the sequences near the twelve SNPs in SEQ ID NO:1, Applicants respectfully submit that the sequence 5'-GCXXXXGC-3', where X may be A, C, T, or G, is not included among the possible 480 decanucleotides. The Patent Office has not indicated otherwise.

Applicants respectfully submit that Pease *et al.* does not anticipate the isolated polynucleotide recited in amended claim 49. Accordingly, Applicants respectfully request that the rejection of claim 49 under 35 U.S.C. § 102(b) be withdrawn.

VIII. CLAIM REJECTION UNDER 35 U.S.C. § 103(a)

A. Claims 53-54, 100, 103-104, 110-112, 114, 116-119 and 123

Claims 53-54, 100, 103-104, 110-112, 114, 116-119 and 123 stand rejected under 35 U.S.C. § 103(a) allegedly as being unpatentable over Brennan (U.S. Patent No. 5,474,796) or Pease *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:5022-5026, either in view of Ahern (1995) *The Scientist* 9:20. Applicants respectfully traverse.

Applicants respectfully submit that when taken alone or combination with Ahern, neither Brennan (U.S. Patent No. 5,474,796) nor Pease *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:5022-5026 teach or suggest each and every limitation of claims 53-54, 100, 103-104, 110-112, 114, 116-119 and 123 required for a p*rima facie* case of obviousness. *See, e.g., In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991); *In re Royka*, 180 U.S.P.Q. 580 (CCPA 1974); MPEP § 2143.03.

Claims 53 and 54 are kit claims that comprise respectively at least one and two isolated polypeptides of amended claim 49. As explained in Section VII above, Brennan merely teaches a decanucleotide having the sequence ATTCTTGTTA that does not appear to be included among the possible 480 decanucleotides encompassed in amended claim 49. The Patent Office has not indicated otherwise. Also as explained in Section VII above, Pease *et al.* teach octanucleotides having the sequences 5'-GCXXXXGC-3', where X may be A, C, T, or G, that do not appear to be included among the possible 384 decanucleotides encompassed in amended claim 49. The Patent Office has not indicated otherwise. Ahern does not teach or suggest any oligonuclotides. Since neither Brennan nor Pease *et al.*, when take alone or combination with Ahern, teach or suggest the isolated polynucleotide of claim 49, Applicants respectfully submit that the rejection of claims 53 and 54 is improper an should be withdrawn.

Claims 100 and 123 have been amended to recite oligonucleotides that compromise at least 18 bases. None of Brennan, Pease *et al.*, or Ahern, taken alone or combination, teach or suggest an oligonucleotide compromising at least 18 bases. Therefore, the rejection of claims 100, 123, and claims 103-104, 110-112, 114, 116-119 is improper.

For the above reasons, Applicants respectfully request that the rejection of claims 53-54, 100, 103-104, 110-112, 114, 116-119 and 123 under 35 U.S.C. § 103(a) be withdrawn.

B. Claims 100, 102, and 103

Claims 100, 102, and 123 stand rejected under 35 U.S.C. § 103(a) allegedly as being obvious over Feder *et al.* (U.S. Patent No. 5,872,237) (the parent to the instant application) in

view of Ahern (1995) *The Scientist* 9:20. The Patent Office acknowledges that this rejection might be overcome by, *inter alia*, filing a terminal disclaimer together with an oath or declaration pursuant to 37 C.F.R. § 1.130(a). Indeed, a terminal disclaimer and terminal disclaimer fee authorization were previously mailed January 31, 2001 to the Patent Office along with the Amendment in reply to the Office Action mailed July 31, 2000. Therefore, this rejection is moot. Applicants respectfully request that the rejection of claims 100, 102 and 123 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants respectfully request that the Patent Office reconsider this application with a view towards allowance.

No fees, other than those for an extension of time, are believed to be due with this Amendment and Response. However, the Commissioner is hereby authorized to charge any required fee(s) to Jones Day Deposit Account No. 503013 (order no. 043018-999057).

Respectfully submitted,

Date: June 23, 2004

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